Erlotinib-related skin toxicities: Treatment strategies in patients with metastatic non-small cell lung cancer

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Skin toxicities are the most common side effects associated with the epidermal growth factor receptor inhibitor erlotinib, occurring in most patients receiving the drug. Clinical trials evaluating erlotinib for the treatment of non-small cell lung cancer have reported a range of skin disorders, the most common being acneiform rash, xeroderma (dry skin), pruritus, and paronychia. Although in the majority of cases these effects are mild and transient, they can have a considerable impact on a patient's quality of life and, if particularly severe and persistent, may necessitate treatment interruption or cessation and compromise treatment outcome. This coupled with recent evidence to suggest a positive correlation between the incidence and severity of rash and clinical outcome among erlotinib-treated patients with advanced or metastatic non-small cell lung cancer highlights the importance of adequately managing epidermal growth factor receptor inhibitor–related skin disorders. Clear treatment strategies are therefore necessary to ensure the prevention and optimal management of erlotinib-related skin toxicities thereby enabling patients to continue erlotinib treatment. In this review we present a practical approach for the treatment of erlotinib-related cutaneous side effects in Japanese patients with advanced non-small cell lung cancer providing details of specific treatment interventions, according to symptom severity, for each of the common skin disorders. In addition, the importance of preventive skin care measures—namely maintaining cleanliness, moisturization, and protection from external stimuli—in preventing the development of serious skin disorders is discussed and guidelines for the practice of proper skin care are presented. (J Am Acad Dermatol 2013;69:463-72.)

Key words: acneiform rash; cutaneous side effects; epidermal growth factor receptor inhibitor; erlotinib; Japanese patients; non-small cell lung cancer; prevention; skin toxicities.

In recent years, targeted therapy directed at the epidermal growth factor receptor (EGFR) has emerged as an important therapeutic option for the treatment of patients with a range of solid tumors including non-small cell lung cancer (NSCLC). Erlotinib is a highly selective oral tyrosine kinase inhibitor that targets EGFR to inhibit tumor cell growth and proliferation.[1] Based on the results of 1 international phase III study (BR.21) and 2 Japanese phase II studies, erlotinib monotherapy has received regulatory approval in Europe, the United States, and Japan for the treatment of patients

Abbreviations used:

ADL:	activities of daily living
AEs:	adverse events
BSA:	body surface area
CI:	confidence interval
CRC:	colorectal cancer
EGFR:	epidermal growth factor receptor
FTUs:	fingertip units
HR:	hazard ratio
NSCLC:	non-small cell lung cancer
OS:	overall survival
STEPP:	Skin Toxicity Evaluation Protocol with Panitumumab
UV:	ultraviolet

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with locally advanced or metastatic NSCLC who have failed at least 1 previous chemotherapy regimen.[2-4]

Dermatologic side effects are relatively common among patients treated with EGFR inhibitors.[5,6] These skin disorders are generally mild or moderate in severity and can be managed by appropriate interventions or by reducing or interrupting the erlotinib dose. Appropriate and timely management make it possible to continue a patient's quality of life and maintain compliance; however if these adverse events (AEs) are not managed appropriately, and become more severe, treatment cessation may be warranted compromising clinical outcome. Evidence has emerged in recent years to suggest that the incidence and severity of rash are positively correlated with treatment outcome among patients receiving erlotinib (Fig 1).[7-12] Strategies to improve the assessment and management of EGFR-related skin AEs are therefore essential to ensure compliance with anticancer therapy, thereby enabling patients to achieve optimal benefits. The purpose of this article is to describe the most common erlotinib-related skin disorders in patients with advanced/metastatic NSCLC and to provide treatment strategies for their management.

CAPSULE SUMMARY

- Skin toxicities are a common side effect of the epidermal growth factor receptor inhibitor erlotinib.
- We present a practical approach for the treatment of erlotinib-related cutaneous side effects including treatment interventions according to symptom severity and the importance of preventive measures.
- Skin toxicities impact quality of life and may necessitate treatment interruption. Ensuring the prevention and optimal management of erlotinib-related skin toxicities will enable erlotinib treatment continuation to gain the best outcome.

ERLOTINIB-RELATED SKIN DISORDERS: SYMPTOMS AND INCIDENCE

Common skin disorders with erlotinib

The most frequently occurring skin disorders reported with erlotinib are acneiform rash, xeroderma (dry skin), pruritus, and paronychia (periungual inflammation). Skin disorders have been generally categorized by the Common Terminology Criteria for AEs v4.0 (Table I), with special criteria for paronychia being adopted because there is no Common Terminology Criteria for AEs category for paronychia. Erlotinib-related acneiform rash typically manifests as red papules and/or pustules on the face, chest, abdomen, or thighs (Fig 2). Several features distinguish an acneiform rash from acne vulgaris, including the absence of bacterial infection.[13] Xeroderma is characterized by dryness and roughness of the skin, and scaling (Fig 2). The scales may be associated with inflammatory erythema or pigmentation. As the condition progresses, fissures appear and the skin becomes itchy and similar to pityriasis, resembling fish scales; the fissures can cause considerable pain. Pruritus, or skin itching, usually develops with xeroderma or dermatitis; it is unusual for a patient to present with pruritus without a rash. Pruritus may cause patients to scratch, resulting in scratch marks, lichenification, and eczematous inflammation with hyperpigmentation and/or secondary infection. Paronychia manifests as dusky erythema around several fingernails and toenails (Fig 3). This results in the formation of painful fissures, swelling, and noninfectious granulation. Bleeding or exudation can result in crust formation, which may be extremely painful and severely impact quality of life. Secondary infection arising from paronychia is also a common problem.

Incidence of the most common skin disorders

Data from a Japanese postmarketing surveillance study of erlotinib-treated patients with NSCLC (POLARSTAR; n = 3488) revealed a high incidence of rash (63%), with somewhat lower incidences for dry skin, pruritus, and paronychia (7.7%, 3.8%, and 6.0%, respectively).[14] The majority of the skin disorders were grade 1 (mild) or grade 2 (moderate) in severity; just 6.7% of rash cases were grade 3 or higher, and 0.2% of dry skin and pruritus episodes and 0.7% of paronychia cases were grade 3 or higher in the surveillance study (Table II).[14,15]

Time of onset typically varies according to the type of skin disorder. In the POLARSTAR study, median time to onset was shortest for rash (8 days, range 1-494) and longest for paronychia (32 days, range 2-558); median time to onset for dry skin and pruritus were 15 days and 11 days, respectively (Table II).[14] These findings are generally comparable with those from the 2 phase II studies for rash (median 6 days), pruritus (median 7 and 9 days), dry skin (12 and 23 days), and paronychia (41.5 and 49.5 days).[16]

TREATMENT STRATEGIES FOR ERLOTINIB-RELATED RASH

Published evidence

Few randomized controlled trials have been conducted in the management of EGFR-related skin disorders; 5 have been published to date although each study is small.[17-21] The studies were

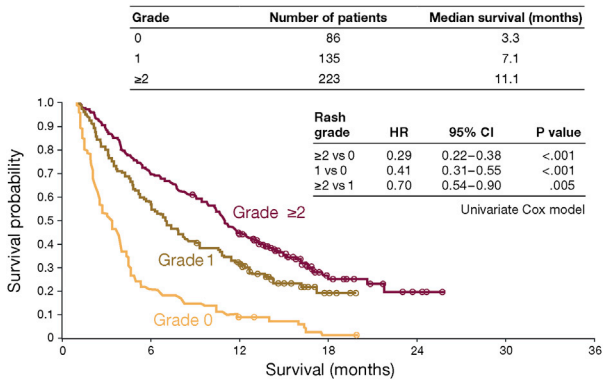

Fig 1. Rash emergence, severity, and survival. Relationship between these in BR.21 study.[11] *CI*, Confidence interval; *HR*, hazard ratio. Reprinted from Clinical Cancer Research 2007;13(13):3913-22, Wacker B et al, Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies, with permission from AACR.

in different cancer types (including lung) with a range of EGFR inhibitors (cetuximab, panitumumab, erlotinib, gefitinib) and investigated the use of prophylactic or reactive treatments (Table III). Of these studies, 2 generated positive findings.

The most persuasive results were seen in the open-label phase II Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) trial in patients with metastatic colorectal cancer. Patients receiving therapy including the EGFR inhibitor panitumumab were randomized to pre-emptive treatment (n = 48, comprising emollients, sunscreen, topical steroid, and doxycycline) or reactive treatment (n = 47) after skin toxicity developed. Notably, the primary endpoint, the incidence of specific grade 2 or higher skin toxicities during the 6-week skin treatment period, was reduced by more than 50% in the pre-emptive group compared with the reactive group (62% vs 29%; odds ratio 0.3; 95% confidence interval 0.1-0.6) (Fig 4).[21]

In a randomized, double-blind trial of prophylactic oral minocycline in patients with metastatic colorectal cancer, patients receiving cetuximab were randomized to receive oral minocycline 100 mg once daily or placebo for the first 8 weeks of therapy. Up to week 4, mean lesion count in the oral minocycline group was half that of the placebo group ($P = .005$), but by week 8 the placebo group had spontaneously improved, suggesting the effects of prophylactic oral minocycline were most effective on early symptoms.[17]

Several reports into the use of topical retinoids in the treatment of EGFR-induced skin disorders have been published.[22-26] One agent, adapalene (a topical retinoid) has been used successfully to treat paronychia in patients receiving EGFR inhibitors (gefitinib, erlotinib, cetuximab).[25,26] In case studies of 4 patients (1 with lung cancer receiving gefitinib, 1 with lung cancer receiving erlotinib, and 2 with rectal cancer receiving cetuximab) who had developed EGFR-related paronychia of grade 2 or 3, administration of adapalene gel for 2 to 4 weeks led to resolution of the paronychia in each case.[25,26] Adapalene was also reported to reduce severe acneiform eruptions in a cetuximab-treated patient with colorectal cancer.[27] The observations to date provide an option for the treatment of paronychia or acneiform rash when other measures have not been effective.

Interventions by symptom severity

Taking the published reports into account, together with our experience in the Japanese clinical context, we have compiled an algorithm (Fig 5) that will support patients and physicians in the management of their EGFR-related skin disorders. The algorithm provides guidance for the diagnosis and treatment of the 3 most common erlotinib-related skin disorders: acneiform rash, xeroderma, and paronychia. Because such skin disorders are usually aseptic, topical steroids and emollients are the mainstay of treatment. However, if the skin disorder persists, secondary infection may occur requiring the use of antibiotics. Oral minocycline may be prescribed with the expectation that it will have an anti-inflammatory effect without infection during grade 2. If a patient develops a grade 3 acneiform rash, xeroderma, pruritus, or grade 2 or higher paronychia they should be referred to a dermatologist.

Five classes of topical steroid are currently marketed in Japan based on their anti-inflammatory potency: weak; medium; strong (eg, betamethasone valerate/beclomethasone dipropionate); very strong (eg, betamethasone butyrate/dexamethasone propionate); and strongest (eg, clobetasol propionate and diflorasone diacetate). Only topical steroids with a potency ranking of strong or above are recommended for the management of erlotinib-related rash (Fig 5). Topical steroids are available as ointments, creams, lotions, and tapes; choice of formulation should be determined by the type of skin lesion. Treatment should be initiated soon after the emergence of a skin disorder and ongoing treatment may be necessary for several weeks.

Emollients include oleaginous ointments (white petroleum jelly), urea preparations, and heparinoids. They should be applied after hand washing, and immediately after showering or bathing, to susceptible areas (eg, face, chest, and back) and to areas that dry easily (eg, trunk, hands, and feet).

For both topical steroids and emollients, fingertip units (FTUs) should be used as the guideline for the

Table I. Symptoms and interventions of most common erlotinib-related skin disorders by severity

Event	Grade 1	Grade 2	Grade 3*	Grade 4*
Acneiform rash	Papules and/or pustules covering <10% BSA, with/without symptoms of pruritus or tenderness	Papules and/or pustules covering 10%-30% BSA, with/without symptoms of pruritus or tenderness; associated with psychosocial impact, and limiting instrumental ADL	Papules/pustules covering >30% BSA with/without symptoms of pruritus or tenderness; limiting self-care ADL associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any percent of BSA with/without symptoms of pruritus or tenderness; associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences
	Topical steroids (twice daily) Face: medium/strong class Other areas: strong class	Topical steroids Face: strong class Other areas: at least very strong class + oral minocycline† (50 mg twice daily)	Topical steroids All areas: at least very strong class + oral minocycline† + oral steroids (prednisolone 10 mg for 1 wk)	Refer for admission to major hospital with dermatology specialists Note: handling of cases such as Stevens-Johnson syndrome or toxic epidermal necrolysis requires specialist care

	Grade 1	Grade 2	Grade 3*
Xeroderma (dry skin)	Covering <10% BSA, without erythema or pruritus Emollients (heparinoids, petroleum jelly, urea preparations‡)	Covering 10%-30% BSA, with erythema or pruritus; limiting instrumental ADL Emollients + Topical steroids (at least strong class)	Covering >30% BSA, with pruritus; limiting self-care ADL
Pruritus	Mild or localized; topical treatment required	Intense or widespread; intermittent; skin changes caused by scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroids or immunosuppressants indicated
	Emollients + topical steroids (at least strong class)	Emollients + topical steroids (at least strong class) + oral antihistamines or oral antiallergy medicines	
Paronychia§//	Nailfold edema or erythema; disruption of cuticle	Localized intervention indicated; oral intervention indicated (eg, antibiotic, antifungal, antiviral); nailfold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self-care ADL
	Washing + cooling¶ + topical steroids (at least strong class) + emollients + taping	Washing + cooling + topical steroids (at least very strong class) + emollients + taping or cryotherapy (liquid nitrogen) + oral minocycline; if there is fissuring, flurandrenolide tape	Washing + cooling Grade 2 treatments/partial nail removal/artificial nail placement

Skin disorders are graded according to Common Terminology Criteria for Adverse Events v4.0.[13]
ADL, Activities of daily living; *BSA*, body surface area; *IV*, intravenous.
*Refer to dermatologist promptly.
†Switch to macrolide antibiotic if dizziness occurs.
‡Can cause burning or stinging in areas with fissuring.
§If grade ≥2 refer to dermatologist promptly.
//Paronychia severity is graded according to criteria prepared by editorial committee of Erlotinib Rash Management Overview and Specific Treatment Guidelines v3.0.
¶Water or gel-type cooling agent should be used to cool entire area.

Fig 2. Acneiform rash and xeroderma. Characteristic symptoms.

Fig 3. Paronychia. Characteristic symptoms.

Table II. Incidence and time to onset of most common skin disorders in postmarketing surveillance study of advanced non-small cell lung cancer (analysis of 3488 patients in safety data set)[14]

	Incidence, % (n)		Time to onset, d
Event	All grades*	Grade ≥3	Median (range)
Rash	63.0 (2199)	6.7 (234)	8 (1-494)
Dry skin	7.7 (270)	0.2 (8)	15 (1-185)
Pruritus	3.8 (132)	0.2 (6)	11 (1-220)
Paronychia	6.0 (210)	0.7 (23)	32 (2-558)

If patient experienced multiple events in same category, grade of most serious episode was used.
*Common Terminology Criteria for Adverse Events v3.0.[15]

amount to be used per application. One FTU equates to approximately 0.5 g for ointments and creams, or an amount from the tip to the first joint of the index finger (for a lotion, 1 FTU is about the size of a coin). One FTU is a suitable amount for covering approximately 2 adult palms (Fig 6).[28,29] Due to concerns regarding the development of adverse reactions with topical steroids (eg, skin atrophy and telangiectasia), unnecessary long-term use of these agents should be avoided.

Acneiform rash

In the event of acneiform rash, strong or very strong topical steroids, or in severe cases (grade 2/3) the strongest class of topical steroids, should be applied twice daily (Table I). Once symptoms have improved, the patient should be switched to a medium-class steroid. If symptoms worsen, the patient should be switched to stronger-class steroids. Careful consideration should be given to the degree of skin permeability, and hence the level of drug absorption, of the area of steroid application. Because the skin on the face is highly permeable to steroid drugs, medium-class steroids may be used for patients with a grade 1 acneiform rash on the face. In the case of grade 2 or higher rash, the oral antibiotic minocycline should also be given at a dose of 50 mg twice daily. Detailed recommendations are also described in Table I.

Table III. Randomized controlled trials on management of epidermal growth factor receptor-related skin disorders

Study	EGFR inhibitor	Tumor type	Treatment	Results
Scope et al,[17] 2007	Cetuximab	CRC	Prophylactic oral minocycline 100 mg od vs placebo for 8 wk	Decreased mild/moderate lesion count with minocycline at wk 4 (P = .005)
			Prophylactic tazarotene 0.05% od on left or right side of face for 8 wk	No difference between groups
Jatoi et al,[18] 2008	Various	Various	Prophylactic oral tetracycline 500 mg bd vs placebo for 4 wk	Decrease in grade 2 rash with tetracycline at wk 4 (P = .01); no difference between groups at wk 8 (P = .61)
Scope et al,[19] 2009	Cetuximab	CRC	Reactive topical pimecrolimus 1% bd for 5 wk on left or right sides of face vs no pimecrolimus	Greater decrease in lesion count with pimecrolimus (P < .05)*
Jatoi et al,[20] 2010	Various	Various	Sunscreen (SPF 60) bd vs placebo for 28 d	No difference between treatment groups (P = .36)
Lacouture et al,[21] 2010	Panitumumab	CRC	Prophylactic treatment† vs reactive treatment‡	Decrease in grade ≥2 skin toxicity with prophylaxis (29% vs 62%)

bd, Twice a day; *CRC*, colorectal cancer; *od*, daily; *SPF*, sun protection factor.
*Lesions on both sides of face decreased significantly over study duration, therefore effect was considered not clinically relevant.
†Including skin moisturizer, sunscreen, topical steroid, and oral doxycycline.
‡Any treatment as determined by physician.

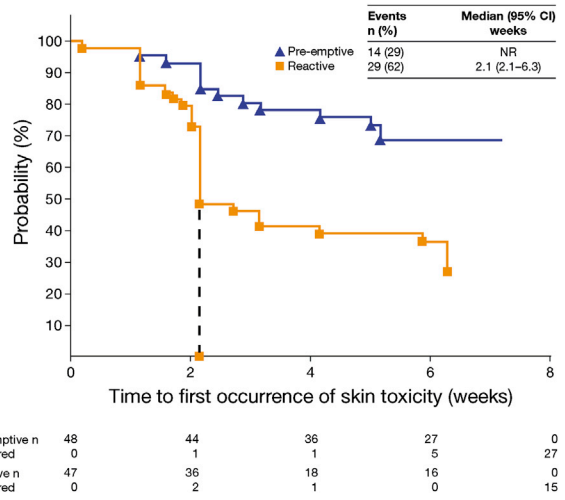

Fig 4. Grade ≥2 skin toxicity in patients with metastatic colorectal cancer (Skin Toxicity Evaluation Protocol with Panitumumab [STEPP] study), time to first occurrence.[21] *CI*, Confidence interval; *NR*, not reached. Reprinted from Lacouture ME et al, Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer, Journal of Clinical Oncology 28(8):1351-7, with permission. © (2010) American Society of Clinical Oncology. All rights reserved.

Xeroderma

Erlotinib-related xeroderma should be treated with emollients, with the addition of a topical steroid (at least strong class) for grade 2 severity or higher (Table I). Patients should be switched to a medium-class topical steroid once symptoms improve. Emollients should be used as soon as possible after bathing to prevent the rapid development of dry skin caused by washing away sebum.

Pruritus

If a patient experiences intense pruritus with an acneiform rash or xeroderma, then emollients plus topical steroids (at least strong class) should be prescribed. Oral antihistamines or oral antiallergy drugs should be used in addition to emollients and steroids for pruritus of grade 2 severity or higher.

Paronychia

The affected area should be washed with soapy water, rinsed well, moisturized, and protected with gauze (Table I). Additional benefit may be provided by cooling the affected area using water or a gel-type cooling agent, taping the affected area using stretchable tape (Fig 7), and applying emollients. Strong or very strong topical steroids plus oral minocycline

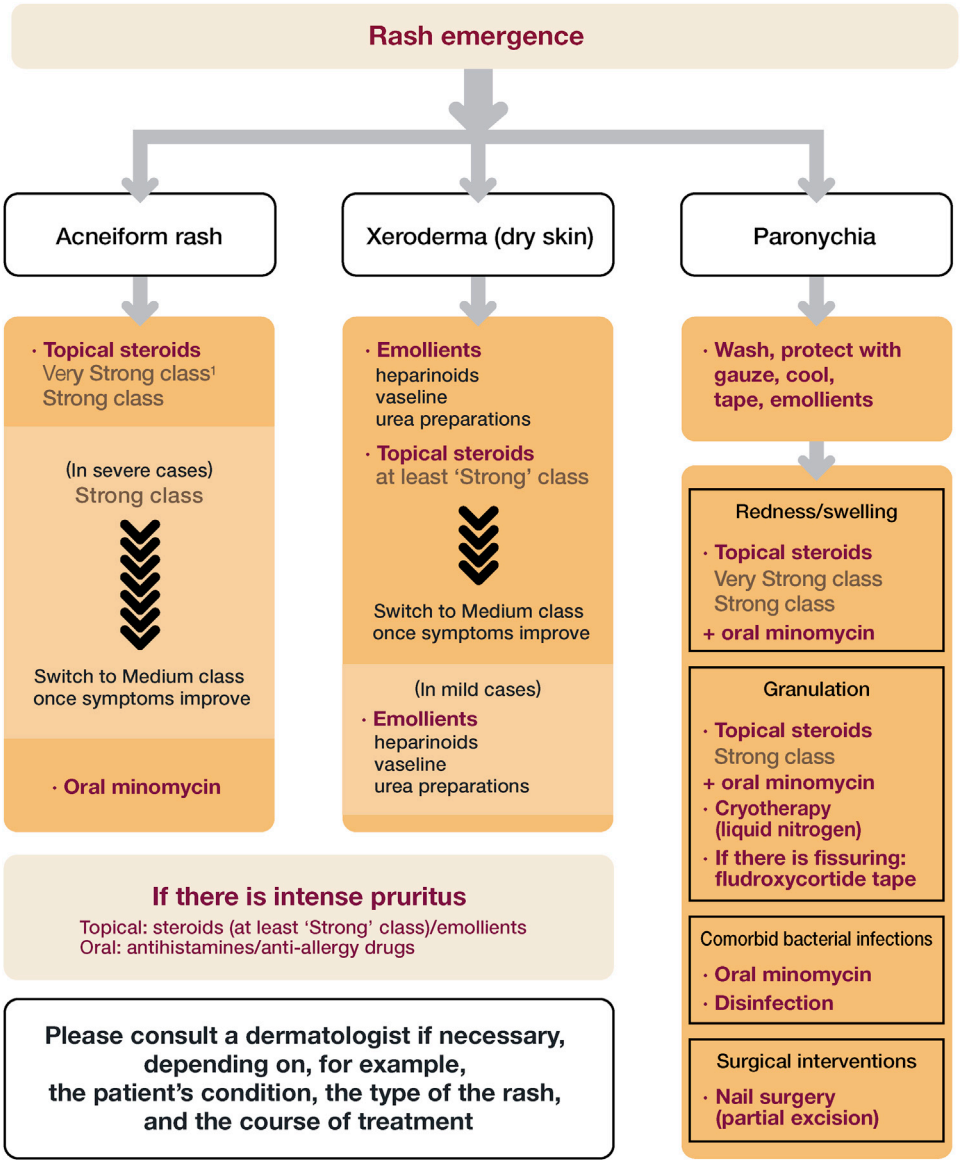

Fig 5. Erlotinib-related skin disorders. Diagnosis and treatment.

should be used to treat redness or swelling. Initial erythema may respond to treatment with just a topical steroid (at least strong class). Treatment recommendations for granulation include the strongest class of topical steroids, oral minocycline, or cryotherapy using liquid nitrogen. In severe cases, surgical treatment involving removal of part of the nail plate is needed (Fig 8). If the patient has a comorbid bacterial infection oral minocycline should be used.

Discontinuation or dose adjustment of erlotinib

Based on experience with erlotinib[2-4] we proposed specific recommendations for the discontinuation or dose adjustment of erlotinib in patients experiencing skin toxicities (Table IV). Erlotinib should be continued at a dose of 150 mg/d for patients experiencing a grade 1 event. This is also the case for grade 2 events unless symptoms do not resolve on symptomatic therapy; in this situation consideration should be given to dose reduction (100 mg/d). Grade 3 skin toxicity requires dose reduction to 50 mg/d; however, treatment interruption should be considered if there is no improvement after the use of potent symptomatic therapy (eg, increasing the dose of topical steroid). If the AE improves to grade 2 or lower, then treatment with erlotinib may be resumed at 100 mg/d. Any patient experiencing grade 4 skin toxicity should permanently discontinue erlotinib therapy.

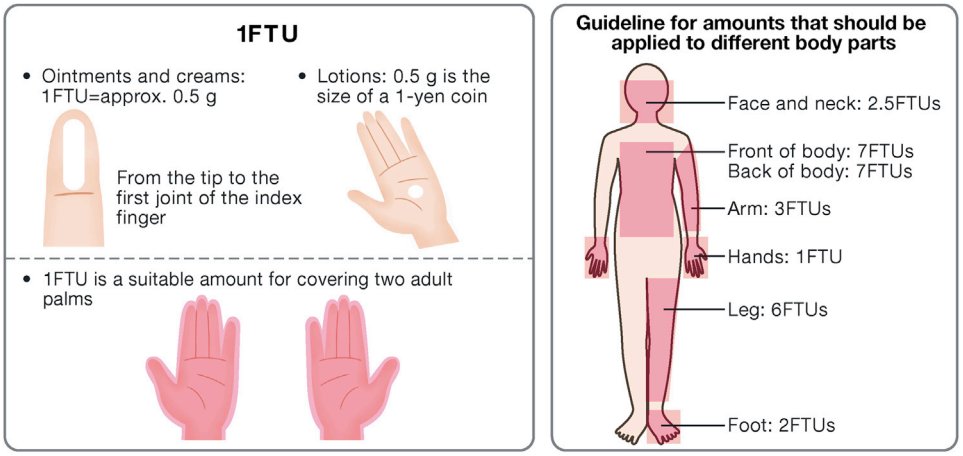

Fig 6. Application of topical creams and emollients: guidance on quantities for application. *FTU*, Fingertip unit.

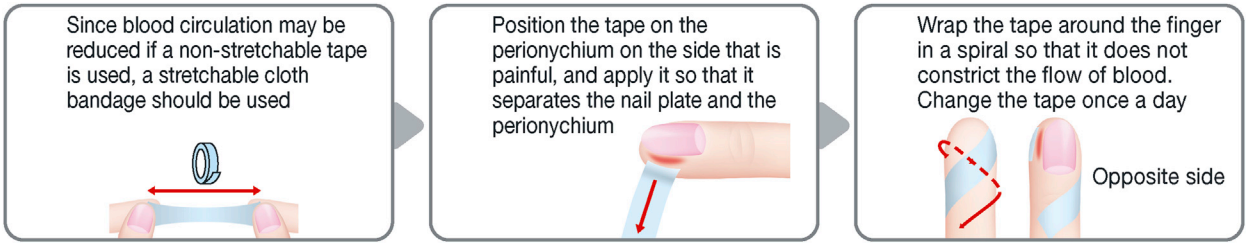

Fig 7. Procedure for using tape to treat paronychia.

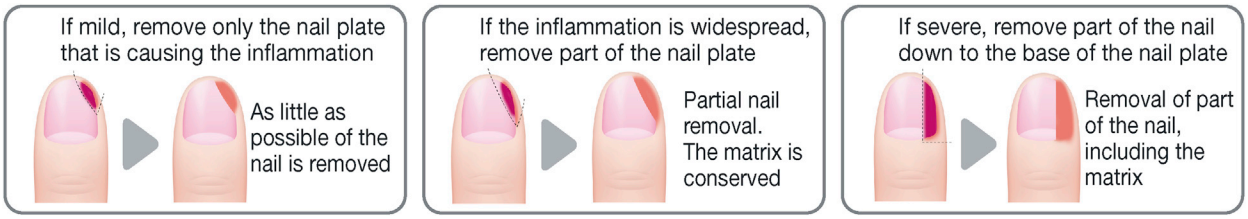

Fig 8. Procedure for removing nail plate and matrix in cases of paronychia.

PREVENTIVE SKIN CARE MEASURES AND PATIENT EDUCATION

When initiating erlotinib therapy it is important to explain to the patient that skin disorders often develop during treatment and that if they experience any skin abnormalities, including on the scalp or around the nails, they should seek prompt medical attention. Preventive skin care may reduce the incidence, and prolong time to onset, of above grade 2 skin disorders and may also reduce severe skin toxicity. This theory is supported by data from the phase II STEPP trial in patients with metastatic colorectal cancer, as described earlier.[21]

These findings emphasize the importance of initiating proper skin care in parallel with drug treatment and continuing this on an ongoing basis to mitigate the development of serious skin symptoms and enable continuation of therapy. All patients should receive appropriate instruction in the fundamentals of proper skin care, which include maintaining cleanliness, moisturization, and protection from external stimuli. Patients should shower or bathe every day using soaps and shampoos that are relatively nonirritating (ie, weakly acidic) and using the quantities indicated on the label; bath salts or additives that contain sulfur are not recommended because they can dry out the skin. The soap should be worked into a good lather (which aids easier dirt removal and is less irritating to the skin) and used to gently wash the skin using the palm of the hand. Any soap or shampoo should be thoroughly rinsed. Drying should be by patting (not rubbing) gently with a clean towel. If a patient experiences severe itchiness they should bath or shower using water that

Table IV. Recommendations for dose adjustment of erlotinib after emergence of skin disorder

Grade 1	Grade 2	Grade 3	Grade 4
Continue at 150 mg	Continue at 150 mg; if patient's condition worsens even with symptomatic treatment (eg, steroid therapy), consider reducing dose to 100 mg	Reduce dose to 50 mg; if improvement is not seen despite more powerful symptomatic therapy, consider interrupting treatment; if event falls to grade ≤ 2 in severity, treatment may be resumed at 100 mg	Permanently discontinue therapy

If treatment was initiated at 100 mg or 50 mg, consideration should be given to reducing dose or interrupting treatment as appropriate.

is not too hot (approximately 37°C in the summer and 39°C in the winter). The education of male patients may be particularly challenging as some men may have a tendency to be unconcerned with skin care, therefore important information should also be given to their family members. The vast range of skin care products marketed today makes it vital that patients receive specific instruction on which products to use and how to use them.

In addition to maintaining skin cleanliness and moisturization it is sensible that patients protect their skin from the sun to avoid ultraviolet (UV). Although Jatoi et al found that there were no differences between treatment groups in the use of sunscreen,[20] there have been reports of individuals whose rash is triggered or exacerbated by UV exposure,[27] therefore sunscreen protection is a sensible precaution. UV protection requires use of a high-factor sunscreen (sun protection factor ≥ 30 and UVA protection grade of at least ++), which should be applied liberally if going outside for an extended period. A sunscreen that is labeled as "nonchemical" and does not contain UV absorbers is recommended as these ingredients can be irritants. Additional tips for avoiding exposure to UV include wearing/using clothing that blocks UV (eg, umbrellas, wide-brimmed hats, sun visors, scarves, gloves, sunglasses, and clothing with few exposed areas).

In addition to understanding the importance of preventive skin care, it is crucial that patients appreciate the importance of using the appropriate doses of topical treatments, particularly steroids. As already discussed, the patient should be educated in the use of FTUs as a guide to the amount of drug that should be used per application (Fig 6).[29,30]

CONCLUSION

Erlotinib is an important therapy for patients with locally advanced or metastatic NSCLC, achieving a significant overall survival benefit when used as second- or third-line treatment. Although generally well tolerated, erlotinib, in common with other EGFR inhibitors, is associated with the development of class-specific cutaneous side effects, which appear to be a surrogate marker for clinical outcome. The mainstay of treatment for the most common skin disorders associated with erlotinib—namely acneiform rash, xeroderma, pruritus, and paronychia—is topical steroids (at least strong class) together with emollients. For patients with paronychia, adapalene is also an option, having been effective for some patients in the treatment of periungual inflammation. Ultimately, by following the management and treatment strategies for erlotinib-related skin toxicities discussed in this review, continuation of erlotinib treatment should be possible for a higher proportion of patients, enabling them to benefit from this promising therapy.

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